AHRQ Healthcare Horizon Scanning System – Potential High-Impact Interventions Report

Priority Area 04: Dementia (Including Alzheimer's Disease)

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Statement of Funding and Purpose

This report incorporates data collected during implementation of the Agency for Healthcare Research and Quality (AHRQ) Healthcare Horizon Scanning System by ECRI Institute under contract to AHRQ, Rockville, MD (Contract No. HHSA290201000006C). The findings and conclusions in this document are those of the authors, who are responsible for its content, and do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

This report's content should not be construed as either endorsements or rejections of specific interventions. As topics are entered into the System, individual topic profiles are developed for technologies and programs that appear to be close to diffusion into practice in the United States. Those reports are sent to various experts with clinical, health systems, health administration, and/or research backgrounds for comment and opinions about potential for impact. The comments and opinions received are then considered and synthesized by ECRI Institute to identify interventions that experts deemed, through the comment process, to have potential for high impact. Please see the methods section for more details about this process. This report is produced twice annually and topics included may change depending on expert comments received on interventions issued for comment during the preceding 6 months.

A representative from AHRQ served as a Contracting Officer's Technical Representative and provided input during the implementation of the horizon scanning system. AHRQ did not directly participate in horizon scanning, assessing the leads for topics, or providing opinions regarding potential impact of interventions.

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None of the individuals compiling this information has any affiliations or financial involvement that conflicts with the material presented in this report.

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Preface

The purpose of the AHRQ Healthcare Horizon Scanning System is to conduct horizon scanning of emerging health care technologies and innovations to better inform patient-centered outcomes research investments at AHRQ through the Effective Health Care Program. The Healthcare Horizon Scanning System provides AHRQ a systematic process to identify and monitor emerging technologies and innovations in health care and to create an inventory of interventions that have the highest potential for impact on clinical care, the health care system, patient outcomes, and costs. It will also be a tool for the public to identify and find information on new health care technologies and interventions. Any investigator or funder of research will be able to use the AHRQ Healthcare Horizon Scanning System to select potential topics for research.

The health care technologies and innovations of interest for horizon scanning are those that have yet to diffuse into or become part of established health care practice. These health care interventions are still in the early stages of development or adoption, except in the case of new applications of already-diffused technologies. Consistent with the definitions of health care interventions provided by the Institute of Medicine and the Federal Coordinating Council for Comparative Effectiveness Research, AHRQ is interested in innovations in drugs and biologics, medical devices, screening and diagnostic tests, procedures, services and programs, and care delivery.

Horizon scanning involves two processes. The first is identifying and monitoring new and evolving health care interventions that are purported to or may hold potential to diagnose, treat, or otherwise manage a particular condition or to improve care delivery for a variety of conditions. The second is analyzing the relevant health care context in which these new and evolving interventions exist to understand their potential impact on clinical care, the health care system, patient outcomes, and costs. It is NOT the goal of the AHRQ Healthcare Horizon Scanning System to make predictions on the future use and costs of any health care technology. Rather, the reports will help to inform and guide the planning and prioritization of research resources.

We welcome comments on this Potential High Impact report. Send comments by mail to the Task Order Officer named in this report to: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to: effectivehealthcare@ahrq.hhs.gov.

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Background

Horizon scanning is an activity undertaken to identify technological and system innovations that could have important impacts or bring about paradigm shifts. In the health care sector, horizon scanning pertains to identification of new (and new uses of existing) pharmaceuticals, medical devices, diagnostic tests and procedures, therapeutic interventions, rehabilitative interventions, behavioral health interventions, and public health and health promotion activities. In early 2010, the Agency for Healthcare Research and Quality (AHRQ) identified the need to establish a national Healthcare Horizon Scanning System to generate information to inform comparative-effectiveness research investments by AHRQ and other interested entities. AHRQ makes those investments in 14 priority areas. For purposes of horizon scanning, AHRQ's interests are broad and encompass drugs, devices, procedures, treatments, screening and diagnostics, therapeutics, surgery, programs, and care delivery innovations that address unmet needs. Thus, we refer to topics identified and tracked in the AHRQ Healthcare Horizon Scanning System generically as "interventions." The AHRQ Healthcare Horizon Scanning System implementation of a systematic horizon scanning protocol (developed between September 1 and November 30, 2010) began on December 1, 2010. The system is intended to identify interventions that purport to address an unmet need and are up to 3 years out on the horizon and then to follow them up to 2 years after initial entry into the health care system. Since that implementation, review of more than 18,000 leads about potential topics has resulted in identification and tracking of about 2,000 topics across the 14 AHRQ priority areas and 1 cross-cutting area; about 550 topics are being actively tracked in the system.

Methods

As part of the Healthcare Horizon Scanning System activity, a report on interventions deemed as having potential for high impact on some aspect of health care or the health care system (e.g., patient outcomes, utilization, infrastructure, costs) is aggregated twice a year. Topics eligible for inclusion are those interventions expected to be within 0–3 years of potential diffusion (e.g., in phase III trials or for which some preliminary efficacy data in the target population are available) in the United States or that have just begun diffusing and that have completed an expert feedback loop.

The determination of impact is made using a systematic process that involves compiling information on topics and issuing topic drafts to a small group of various experts (selected topic by topic) to gather their opinions and impressions about potential impact. Those impressions are used to determine potential impact. Information is compiled for expert comment on topics at a granular level (i.e., similar drugs in the same class are read separately), and then topics in the same class of a device, drug, or biologic are aggregated for discussion and impact assessment at a class level for this report. The process uses a topic-specific structured form with text boxes for comments and a scoring system (1 minimal to 4 high) for potential impact in seven parameters. Participants are required to respond to all parameters.

The scores and opinions are then synthesized to discern those topics deemed by experts to have potential for high impact in one or more of the parameters. Experts are drawn from an expanding database ECRI Institute maintains of approximately 150 experts nationwide who were invited and agreed to participate. The experts comprise a range of generalists and specialists in the health care sector whose experience reflects clinical practice, clinical research, health care delivery, health business, health technology assessment, or health facility administration perspectives. Each expert uses the structured form to also disclose any potential intellectual or financial conflicts of interest

(COIs). Perspectives of an expert with a COI are balanced by perspectives of experts without COIs. No more than two experts with a possible COI are considered out of a total of the five to eight experts who are sought to provide comment for each topic. Experts are identified in the system by the perspective they bring (e.g., clinical, research, health systems, health business, health administration, health policy).

The topics included in this report had scores *and/or* supporting rationales at or above the overall average for all topics in this priority area that received comments by experts. Of key importance is that topic scores alone are not the sole criterion for inclusion—experts' rationales are the main drivers for the designation of potentially high impact. We then associated topics that emerged as having potentially high impact with a further subcategorization of "lower," "moderate," or "higher" within the high-impact-potential range. As the Healthcare Horizon Scanning System grows in number of topics on which expert opinions are received and as the development status of the interventions changes, the list of topics designated as having potentially high impact is expected to change over time. This report is being generated twice a year.

For additional details on methods, please refer to the full AHRQ Healthcare Horizon Scanning System Protocol and Operations Manual published on AHRQ's Effective Health Care Web site.

Results

The table below lists the one topic for which (1) preliminary late-phase clinical trial data were available; (2) information was compiled and sent for expert comment before May 15, 2014, in this priority area; and (3) we received five to eight sets of comments from experts between July 1, 2013, and May 23, 2014. (Seventeen topics in this priority area were being tracked in the system as of May 15, 2014.) This single topic emerged again (as it did in the December 2013 report) as having some potential for higher impact on the basis of expert comments. Readers are encouraged to read the detailed information that follows the Executive Summary.

Priority Area 04: Dementia (Including Alzheimer's Disease)

Topic	High-Impact Potential
1. * Off-label intranasal insulin for treatment of Alzheimer's disease	Lower end of the high-impact-potential range

Discussion

Dementia encompasses a group of brain disorders that causes debilitating declines in intellectual and social functioning, although the bulk of research in this priority area focuses on Alzheimer's disease (AD). The National Institute on Aging (NIA) and other clinical experts regard AD as the most common cause of dementia. Available interventions in this area are predominantly symptom-management options; however, emerging research aims to identify disease-modifying therapies and accurate, early diagnostics for patients with AD.

NIA describes AD as a progressive, irreversible disorder, marked by degraded memory and cognitive abilities that eventually impede a patient's daily functioning; the exact cause is unknown. Neuroanatomic and neurophysiologic research into AD etiology has concentrated on two potential biomarkers: amyloid plaques and neurofibrillary tangles. These are found in the brains of patients with AD. Amyloid plaques purportedly damage neurons in the brain and interfere with normal neuron function. Similarly, researchers hypothesize that neurofibrillary tangles adversely affect neuron function and lead to cell death. Additional research implicates inflammation as a potential trigger of progressive neuron death that is often observed in brains of patients with AD.

Biomarkers are typically not evident in preclinical AD, and behavioral symptoms are often dismissed; however, as the disease progresses, beta-amyloid proteins accumulate abnormally,

leading to plaques, and neurons' functional efficiency declines. In later stages of AD, neural damage and atrophy significantly affect memory-forming and executive function areas of the brain, including the parietal and temporal lobes and the hippocampus.

According to the Alzheimer's Association, over 5 million people in the United States were living with AD in 2013; an estimated 11% of people aged 65 years or older, and 32% of people aged 85 years or older have AD. Recent data from the National Center for Health Statistics places AD as the sixth-leading cause of death in the United States. Although common convention, also used throughout this report, refers to patients as having a diagnosis of AD, available diagnostics can only tentatively identify individuals as "probable" AD patients. Definitive diagnoses can be made only at autopsy through neuroanatomical examination of the brain.

The Horizon Scanning System continues to track several interventions and diagnostics for treating dementia, AD, and associated symptoms. Among the tracked topics are novel biologics targeting pathways and processes hypothesized to underlie AD-related cognitive decline, neuroprotective pharmaceuticals purported to address amyloid plaque accumulation, off-label uses of implantable stimulators, and diagnostics intended to accurately identify patients at presymptomatic stages. In this report, we discuss one medication, an off-label use of intranasal insulin under study to treat AD. Converging evidence suggests that brain insulin may play a role in limiting AD pathogenesis, leading researchers to investigate intranasally delivered insulin as a potential therapy for mild cognitive impairment in AD, also referred to as prodromal AD.

Off-Label Intranasal Insulin for Treatment of Alzheimer's Disease

- **Key Facts**: In clinical trials, intranasally delivered insulin is under study for treating AD. Insulin receptors and insulin-sensitive glucose transporters, responsible for regulating energy metabolism in the central nervous system, are co-located brain regions known to be affected by disease progression in patients with AD. Based on research demonstrating that dysfunctional cerebral insulin signaling may contribute to AD etiology, researchers hypothesize that this intervention may both alleviate AD-related cognitive symptoms and modify disease progression. They hypothesize that intranasal delivery could provide beneficial neuroprotective aspects of insulin, while avoiding insulin's adverse effects on blood glucose levels.

  Research into intranasal insulin's efficacy for treating AD is being advanced by several academic and patient advocacy groups that are investigating various delivery methods and forms of insulin for this indication. Results published from small clinical trials (Craft et al., 2012; Craft et al., 2013) suggest that intranasal insulin may improve some cognitive measures in patients with AD or amnestic mild cognitive impairment; additionally, genetic-screening data (Claxton et al., 2013) support a hypothesis that patients' treatment response may depend on whether they do or do not carry the apolipoprotein e4 allele.

  Ongoing clinical trials are enrolling larger patient populations and may clarify optimal dosages, administration frequency, and insulin formulations for this indication. The largest clinical trial to date is scheduled to conclude in 2015. In the absence of more clinical evidence for treating AD, off-label insulin use may be relatively limited because of its potential risks and limited availability in the necessary form for intranasal delivery. As an additional deterrent to expanded off-label utilization, insulin is not widely sold in prefabricated intranasal delivery packages; it is, however, available in various solution forms, with retail prices ranging from $25 to $260 per 10 mL.
- **Key Expert Comments**: Experts recognized a significant unmet need for effective, disease-modifying treatments for AD, and some stated that intranasal insulin had potential to address

this need. The lack of substantial clinical trial data and unresolved optimal treatment protocols dampened some experts' enthusiasm for the intervention at this time, though. Several experts were unimpressed by the reported clinical trial results and wanted further data from larger clinical trials; this concern may be addressed by ongoing trials.

- **Potential for High Impact**: Lower end of the high-impact-potential range

Dementia (Including Alzheimer's Disease) Interventions

Off-Label Intranasal Insulin for Treatment of Alzheimer's Disease

Unmet need: In 2010, 4.7 million Americans had a diagnosis of Alzheimer's disease (AD); by 2050, this number is predicted to increase to 16 million.[1] According to the U.S. National Institute on Aging, approved AD medications treat disease symptoms only, including progressive cognitive declines. These medications do not change the underlying disease process. Additionally, approved treatments are effective for only some AD patients, and efficacy decreases over time.[2] Therefore, an unmet need exists for effective interventions for this condition. Intranasal insulin, if proven effective, may address this need, and potentially represent a disease-modifying treatment for AD.

Intervention: Research has suggested that insulin may play a role in cognitive deficits in AD.[3] Insulin receptors and insulin-sensitive glucose transporters, which regulate energy metabolism in the central nervous system (CNS) by mediating glucose uptake in cells, are co-located in brain structures that are involved in memory and have been shown to be compromised in patients with AD.[3,4] Insulin resistance has also been associated with increased risk for AD, and patients with AD have shown reduced levels of insulin in their cerebrospinal fluid.[3] Additionally, published studies have shown that administering insulin intravenously or intranasally to patients with AD (while maintaining normal blood glucose levels) improves memory in a dose-dependent manner.[5-8]

When administered intranasally, insulin is delivered directly to the CNS via the olfactory and trigeminal neural pathways, bypassing the blood-brain barrier and reducing systemic exposure to the drug. Intranasal delivery may also circumvent potential adverse blood glucose level changes caused by intravenous administration.[4,9] As a result, the majority of clinical trials investigating insulin for treating AD have tested intranasally delivered insulin.

Initial clinical trials revealed that responses to intranasal insulin in patients with AD may differ depending on whether patients possess apolipoprotein e4 (*ApoE-ε4*), an allele known to be a genetic risk factor for AD. Patients with the *ApoE-ε4* allele show cognitive response to lower doses of insulin than do patients without the allele.[3,10,11] Optimal intranasal insulin dosages for treating AD have not been fully determined; in clinical trials, commonly tested protocols include 20 and 40 IU insulin, delivered intranasally once or twice daily.[12,13]

Clinical trials: Researchers investigating intranasal insulin for treating AD have employed various delivery methods, including needleless syringes inserted into alternating nostrils, a nasal drug electronic atomizer device (ViaNase, Kurve Technology, Inc., Lynnwood, WA), and nasal spray bottles.[3,4,12,14,15] These clinical trials have also tested the efficacy of multiple forms of insulin, including human insulin, insulin detemir, and insulin glulisine.[3,12,14,16]

Craft and colleagues published multiple analyses from a clinical trial (n=104) investigating intranasal insulin efficacy in patients with amnestic mild cognitive impairment (MCI) or mild to moderate AD. Patients were randomly assigned to receive 20 IU or 40 IU intranasal insulin or placebo, administered twice daily for 4 months. Investigators initially reported that intranasal insulin administration improved delayed memory ($p<0.05$; assessed by delayed story recall), preserved caregiver-rated functional ability ($p<0.01$; assessed by Alzheimer's Disease Assessment Scale - cognitive subscale) and conserved patients' general cognition and functional abilities ($p<0.05$, assessed by Alzheimer's Disease Cooperative Study – activities of daily living scale).[12] Secondary analyses of these data demonstrated both gender- and *APOE-ε4* allele carrier-dependent differences in patient response to intranasal insulin. All patients showed cognitive improvements when administered 20 IU intranasal insulin, but only males' cognition improved when given 40 IU intranasal insulin. Additionally, when administered 40 IU intranasal insulin, *ApoE-ε4*-negative men showed cognitive improvements, but *ApoE-ε4*-negative women's cognition worsened. *ApoE-ε4*-positive patients remained cognitively stable when administered this dosage.[11]

A clinical trial (n=58) examining the effects of intranasal insulin detemir, a long-acting insulin form, in patients with MCI or AD also reported *ApoE-ε4* allele carrier-dependent responses. On composite memory measures, patients carrying the *ApoE-ε4* allele improved when administered 40 IU insulin detemir daily, but noncarriers' scores worsened with the same dosage. Working memory measures, however, improved with 40 IU daily insulin treatment regardless of *ApoE-ε4* status.[17]

In 2013, the Alzheimer's Disease Cooperative Study registered the largest randomized, controlled trial (n=240) to date for this intervention to investigate intranasal insulin's efficacy for treating AD and amnestic MCI. This trial, testing the effects of twice-daily 20 IU intranasal insulin administrations on cognition and neuroanatomy, is scheduled to be completed in February 2015.[13]

Manufacturer and regulatory status: Clinical trials of intranasal insulin for treating AD frequently investigate insulin products that have marketing approval from the U.S. Food and Drug Administration (FDA) for treating diabetes, including Humulin® and Humulin R® (Eli Lilly and Co., Indianapolis, IN), and Novolin R® and NovoLog® (Novo Nordisk a/s, Bagsvaerd, Denmark).[18,19] Insulin manufacturers are not leading clinical trials or formally pursuing expanded AD-related indications for their products. As a result, using intranasal insulin to treat AD is an off-label indication.

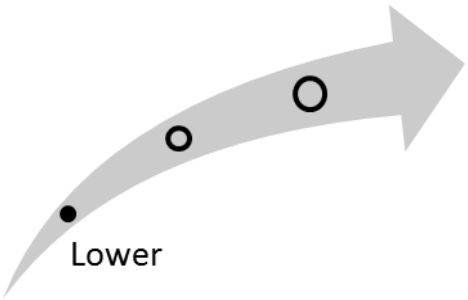
Research groups sponsoring off-label clinical trials include the University of Kansas (Lawrence, KS), the University of Washington (Seattle), the University of Texas at Austin, HealthPartners Institute for Education and Research (Bloomington, MN), the Alzheimer's Research Center at Regions Hospital (St. Paul, MN), and the Alzheimer's Disease Cooperative Study (La Jolla, CA). The latter group is lead sponsor on the largest ongoing trial, a phase II/III trial investigating intranasal administration of Humulin R for treating cognitive symptoms of AD.[13]

Diffusion and cost: Intranasal insulin for treating AD is not sold in prefabricated intranasal delivery packages for this indication, making exact pricing and diffusion difficult to define. Based on ongoing and completed clinical trials, any recommended off-label treatment protocol will involve one or more commercially available forms of insulin. A U.S.-based, online aggregator of prescription-drug prices lists prices ranging from $25 to $250 for a single 10 mL vial of various approved forms of insulin, with human insulin (branded as Novolin R) consistently costing less than either insulin glulisine or insulin detemir.[20-22]

Clinical Pathway at Point of This Intervention

Multiple FDA-approved cholinesterase inhibitors, including donepezil (Aricept®), galantamine (Razadyne®), and rivastigmine (Exelon®) are used to treat symptoms in patients with mild to severe forms of AD;[23] memantine, an N-methyl-D-aspartate receptor antagonist, is approved to treat symptoms of moderate to severe AD.[2] None of these medications, however, has been demonstrated to modify the underlying disease.[2] Intranasal insulin could be used in conjunction with these medications or with other nonpharmaceutical palliative treatments.

Figure 1. Overall high-impact potential: off-label intranasal insulin for treatment of Alzheimer's disease



Experts commenting on this intervention agreed that there is a significant need for additional effective interventions for treating cognitive symptoms of AD, and that intranasal insulin could potentially address this need. As an affordable, easily accessible, and simply administered drug, some experts believed that intranasal insulin could improve patient health improvements while providing cost savings over other AD medications. However, experts' support for this intervention was tempered by the shortage of robust clinical trial data and failure to thoroughly define administration protocols and the ideal population. Some experts were also unconvinced that intranasal insulin would improve patient health outcomes, because it may treat only one aspect of AD, without affecting other aspects of disease progression. Based on this input, our overall assessment is that this intervention is in the lower end of the high-potential-impact range.

Results and Discussion of Comments

Six experts, with clinical, research, and health devices backgrounds, offered perspectives on this intervention.[24-29] We have organized the following discussion of expert comments by the parameters on which they commented.

Unmet need and health outcomes: A significant, unmet need exists for disease-modifying treatments for AD, experts agreed, but were widely divided on the potential for intranasal insulin treatments to address this need. Several experts stated that reported clinical trial data failed to demonstrate that this intervention delays or prevents AD progression.[24,27,29] These experts also were concerned that the few positive trial results were limited in scope and did not sufficiently validate intranasal insulin as superior to approved AD medications. Research has yet to establish optimally effective doses, administration regimens, or ideal patient populations, noted experts. Additionally, multiple experts expressed reservations regarding intranasal insulin's potential to improve patient health outcomes, noting that, if used as adjunctive treatment, the impact would likely be muted.[26,27,29]

Acceptance and adoption: Experts anticipated that, if demonstrated effective, intranasal insulin would be widely accepted by both patients and clinicians, given the lack of other disease-modifying treatments.

Health care delivery infrastructure and patient management: Experts' consensus was that using intranasal insulin for treating AD would have little impact on health care delivery infrastructure because it can be administered in a home or residential care environment without posing additional monitoring and management burdens. Two experts with research backgrounds also indicated that, if this intervention were effective and diffused widely, health care infrastructure demands might be reduced, as patients might be able to live self-sufficiently, or with minimal oversight, for longer periods.[26,28]

Health disparities: Experts noted that insulin is widely available and relatively inexpensive, potentially reducing health disparities. Even if prescribed as an adjunct to other medications, experts

remarked, any additional cost would be outweighed by the potential long-term cost savings that might be realized if intranasal insulin modifies AD progression or significantly improves patient quality of life.

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